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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,272	10/05/2004	Charles Howard Mitch	X-15578	1629

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EXAMINER	
PERLINGER, SARAH E	

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 07/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/510,272	MITCH ET AL.	
	Examiner	Art Unit	
	Sarah E. Perlinger	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11 and 12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11 and 12* is/are rejected.

7)☒ Claim(s) *8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/05/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-9, 11-12 are pending. Claim 10 was cancelled in the preliminary amendment filed on October 5, 2004.

2. ***Oath/Declaration***

It does not state that the person making the oath or declaration has reviewed and understands the contents of the specification, including the claims, as amended by any amendment specifically referred to in the oath or declaration.

3. ***Claim Objections***

Claim 8 is objected to because of the following informalities: claim 8 improperly depends from claim 6. Claim 8 further limits "Related Diseases" wherein claim 6 does not mention "Related Diseases". Appropriate correction is required.

4. ***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 9, 11-12 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki,* 153 USPQ 678 (Bd. App. 1967) and *Clinical Products, Ltd. V. Brenner,* 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

5. ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 9, 11-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 9, 11-12 provide for the use of a compound of formula I, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delineating how this use is actually practiced.

6. Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The scope of claim 7 cannot be ascertained because the claim is self-conflicting. Claim 7 is self-conflicting because a perfectly healthy individual would not be given a compound of formula I. A compound of formula I would not be required unless an individual had already been diagnosed with a disease wherein the compound was necessary. There is no such thing as denovo prevention. It is unclear what the term, "prevention" means. Therefore, the scope of claim 7 cannot be ascertained.

7. Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claim is indefinite where a method of treating "obesity" and "Related Diseases" is claimed. Obesity is a subjective term, what may be obese to one person is not necessarily obese to another. Also, it is unclear what diseases would be related to obesity because no definition of "related" is given. It is unclear how diseases would be related to obesity and what is considered obese and therefore the scope of claim 7 cannot be ascertained because the diseases to be treated cannot be determined.

8. Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claim is indefinite where a method of treating or preventing diabetes is claimed. There are several types of diabetes (i.e. diabetes mellitus, diabetes insipidus, etc.). A compound that may treat one type of diabetes would not necessarily treat another type of diabetes. It is unclear what types diabetes are included and excluded by the term "diabetes".

9. Claims 4-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4-5 are self-conflicting. Please note that the dosage of the composition of claims 4-5 cannot be ascertained because an "effective amount" cannot be determined when it is unclear what result is intended to achieve i.e. active against what. Furthermore, a pharmaceutical composition can neither be ineffective nor toxic, therefore an amount of a compound of formula I should be specified.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in the MPEP 2164.01(a) "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." The factors to be considered herein are those set forth as the In re Wands, 8 USPQ 2nd 1400 (1988) decision.

Nature of Invention

Claim 7 is drawn to a method of treating or preventing obesity and Related Diseases.

The State of the art and Predictability

The state of the art in treating obesity through pharmacological intervention remains controversial and unpredictable. "The effectiveness of interventions to prevent and treat obesity in adults remains unclear, although behavioural therapy and multi-component strategies may be useful...Pharmacological interventions appear to be effective for up to 9 months, after which regain occurs" (Glenny et al., *International Journal of Obesity and Related Metabolic Disorders-Journal of the International Association for the Study of Obesity*, 1997, 21(9), see summary). "The methods used to treat obesity are controversial, some of them lacking appropriate evaluation" (Martin et al., *Southern Medical Journal,* 1995, 88(9), see summary). Finally, the use of potent opioid antagonists in the treatment of obesity has produced conflicting results, "In contrast, naltrexone or nalmaefene, potent opioid receptor antagonists following oral administration, had only marginal effects on food consumption and weight loss in humans" (Mitch et al., *J. Med. Chem.,* 1993, 36, page 2842, introduction).

The amount of guidance and working examples

The specification is limited to *in vitro* opioid binding assays and a short-term *in vivo* food consumption test in male Long-Evans rats. A short-term *in vivo* test of food consumption in Long-Evans rats does not provide description or enablement for treatment of obesity in any patient in need thereof. No nexus between a particular IC50 value and treating obesity was provided. *In vitro* measurement of test compounds' ability to bind and/or act as an antagonist for opioid receptors, does not provide enablement or support the scope of the instant claims treating obesity in any patient in need thereof. The *in vitro* assays do not provide description or enablement for treatment of obesity in any patient in need thereof for which dosage, site of administration and the length of time for which a

compound is administered, must be made known to one having ordinary skill in the art to practice such method. Section 112 requires the application itself to inform, not for others to fine out by themselves. Ex parte Aggarwal 23 USPQ 2nd 1481. In re Gardner 166 USPQ 138.

11. Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in the MPEP 2164.01(a) "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." The factors to be considered herein are those set forth as the In re Wands, 8 USPQ 2nd 1400 (1988) decision.

Nature of Invention

Claim 8 is drawn to a method for treating such a diversity of disorders for example as diabetes, diabetic complications, hyperlipidemia, atherosclerosis, hyperlipoproteinamia, etc. in a patient in need thereof comprising administering a therapeutically effective amount of a compound of formula 1. No nexus exists among the diversity of such disorders which have multiple and unrelated etiology.

The State of the art and Predictability

The current state of the medical art is disease and symptom-oriented, for example, treating diabetes mellitus is analogous to treating impaired glucose tolerance and treating hyperlipidemia is analogous to lowering serum lipid content, etc. Examples for insufficient description and enablement for the claimed scope is treating atherosclerosis, which is a multi-factorial disease and diabetic complications.

It is well recognized by physicians that treating diabetes and treating diabetic complications are separate and unrelated interventions. While diabetes and diabetic complications can occur in the same individual, the medicinal art has a clear understanding that treating diabetes and treating diabetic complications are separate interventions and are not at all related. A method of treating diabetes, ordinarily is analogous to lowering blood glucose or treating the hyperglyceric state of the individual. Treating diabetic complications are "complication" specific and are an independent intervention. There is no evidence that treating diabetic retinopathy would have any impact on treating diabetic neuropathy. It is well documented in the medicinal art that each diabetic complication is an independent intervention and efficacy toward on has no universal extrapolation to all. In addition, the best patient has no gurantee of preventing complications, "Since many conscientious patients, even with the best effort, still develop retinopathy, numerous therapies, including various vitamins, dietary alterations, and hormones, have been used without effort" (see Wyngaarden et al. *Textbook of Medicine,* page 1061).

The development of atheroma is a complex process involving many factors, injury, response, etc. The criticality in determining atherosclerosis development is not solely on one factor alone (e.g. plasma cholesterol level, etc.). The state of the art in atherosclerosis treatment is extremely controversial and the complete pathology of atherosclerosis remains unknown. "Our full understanding of atherosclerosis and our ability to prevent its sequellae are incomplete" (see summary of Heinonen, *Current Atherosclerosis Reports,* 2002, 4(1), 65-70). "Experimental studies have shown the regression of atherosclerosis in animals given a cholesterol-rich diet and then given a normal diet or hypolipidemic therapy. Despite favourable results of clinical trials of primary prevention modifying

the lipid profile, the concept of atherosclerosis regression in man remains very controversial" (see summary of Thomas et al., *Archives des Maladies du Coeur et des Vaisseaux*, 1992, 85, III, 47-57).

The amount of guidance and working examples

The specification is limited to a description of the instant claimed compound's activity in *in vitro* opioid binding assays and provided no nexus for the compounds to have either blood sugar lowering activity or any other efficacy toward the other known complication for diabetes, or blood lipids or any down stream outcome for uncontrollable hyperlipidemia such as atherosclerosis (see Specification, pages 14-18). *In vitro* measurement of test compounds' ability to bind and/or act as an antagonist for opioid receptors, does not provide enablement or support the scope of the instant claims treating diabetic complications, diabetes, atherosclerosis etc. in any patient in need thereof. The *in vitro* assays do not provide description or enablement for treatment of diabetes, hyperlipidemia, atherosclerosis, diabetic complications, etc. in any patient in need thereof for which dosage, site of administration and the length of time for which a compound is administered, must be made known to one having ordinary skill in the art to practice such method. Section 112 requires the application itself to inform, not for others to fine out by themselves. Ex parte Aggarwal 23 USPQ 2nd 1481. In re Gardner 166 USPQ 138.

12. Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in the MPEP 2164.01(a) "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the

enablement requirement and whether any necessary experimentation is "undue." The factors to be considered herein are those set forth as the In re Wands, 8 USPQ 2nd 1400 (1988) decision.

Nature of Invention

The instant claim is drawn to a method for blocking mu, kappa, delta or receptor combination thereof in mammals.

The State of the art and Predictability

It is well known in the art that the opioid receptor is not a single receptor, but rather a family of receptors (see CA 130:346635). The function of opioid receptors is extremely complex and varies throughout different physiological states (see CA 127:341842). Furthermore, other central and peripheral processes may mediate opioid receptor action (see CA 126:54900). It is evidenced throughout the art that the method of manipulating receptor binding, thus subsequently affecting receptor function, is a very complex process with no predictability or generalization.

The amount of guidance and working examples

The specification is limited to a description of *in vitro* assays which measure compound binding activity to the opioid receptors (see Specification, pages 14-18). In absence of any specific substantial support for a specific opioid receptor subtype with a specific testing procedure, multiple assay procedures for diversified receptors, does not teach one having ordinary skill in the art, how to operate the method without undue experimentation. The disclosure lacks description or data as to correlate any property of receptor function with any particular compound. In view of the diversity of multiple utilities as illustrated on page 3, and the high degree of complexity and unpredictability for the opioid receptor family known in the art, one of ordinary skill in the art would not be able to use the compounds in the instant claimed method.

13. ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mitch et al. (see *J. Med. Chem.*, 1993, 36(20), page 2843, compound 11) in view of Armer et al. (see EP 1072592, pages 2-5).

Determination of the scope and content of the prior art (MPEP§ 2141.01)

Mitch et al. disclosed structurally similar piperidine compounds for use as opioid receptor antagonists (see *J. Med. Chem.*, 1993, 36(20), page 2843, compound 11).

Ascertainment of the difference between the prior art and the claims (MPEP § 2141.02)

The difference between the instant claimed compound and the reference compound is that instead of having a hydroxyl substituent at the meta position of the phenyl ring relative to the piperidine, the instant claimed compound has a C(O)NH2 group. Armer et al. however, disclosed a structurally similar piperidine compound wherein the substituent at the meta position of the phenyl group relative to the piperidine ring could be hydroxyl or C(O)NH2, demonstrating the interchangeability of the two moieties (see EP 1072592, page 2 wherein A=single bond and page 4, lines 30-45).

Finding of prima facie obviousness-rationale and motivation (MPEP § 2142-2143)

One having ordinary skill in the art in possession of Mitch et al. and Armer et al. would be in possession of such modification as a C(O)NH2 group at the meta position of the phenyl group relative to the piperidine ring **because** such modification has been clearly guided to one skilled in the art in

these references by exemplification of other analogous compounds. Both references teach structurally similar piperidine compounds which have utility in binding opioid receptors (see *J. Med. Chem.*, 1993, 36(20), page 2842, abstract and EP 1072592, page 2, lines 3-4). Furthermore, Armer et al. demonstrated success in using the structurally similar piperidine compounds in binding opioid receptors (see EP 1072592, page 28, lines 35-40). One having ordinary skill in the art would be motivated to make such modification as a C(O)NH2 substituent at the meta position of the phenyl relative to the piperidine ring, knowing that reasonable success has been demonstrated in analogous compounds. It is prima facie obvious to modify one known compound with attributes proven in analogous compounds.

14. ***Conclusion***

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Sarah E. Perlinger, whose telephone number is (571) 272-5574. The examiner can normally be reached on Monday through Friday, 8:30 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Thomas McKenzie, can be reached at (571) 272-0670. The fax number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DP

07/03/2006

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